# The future is open – improving the utility of preclinical research

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**@camarades_**

# Disclosures

- **BMJ Open Science** (Editor-in-Chief)
  - I receive an honorarium for this role

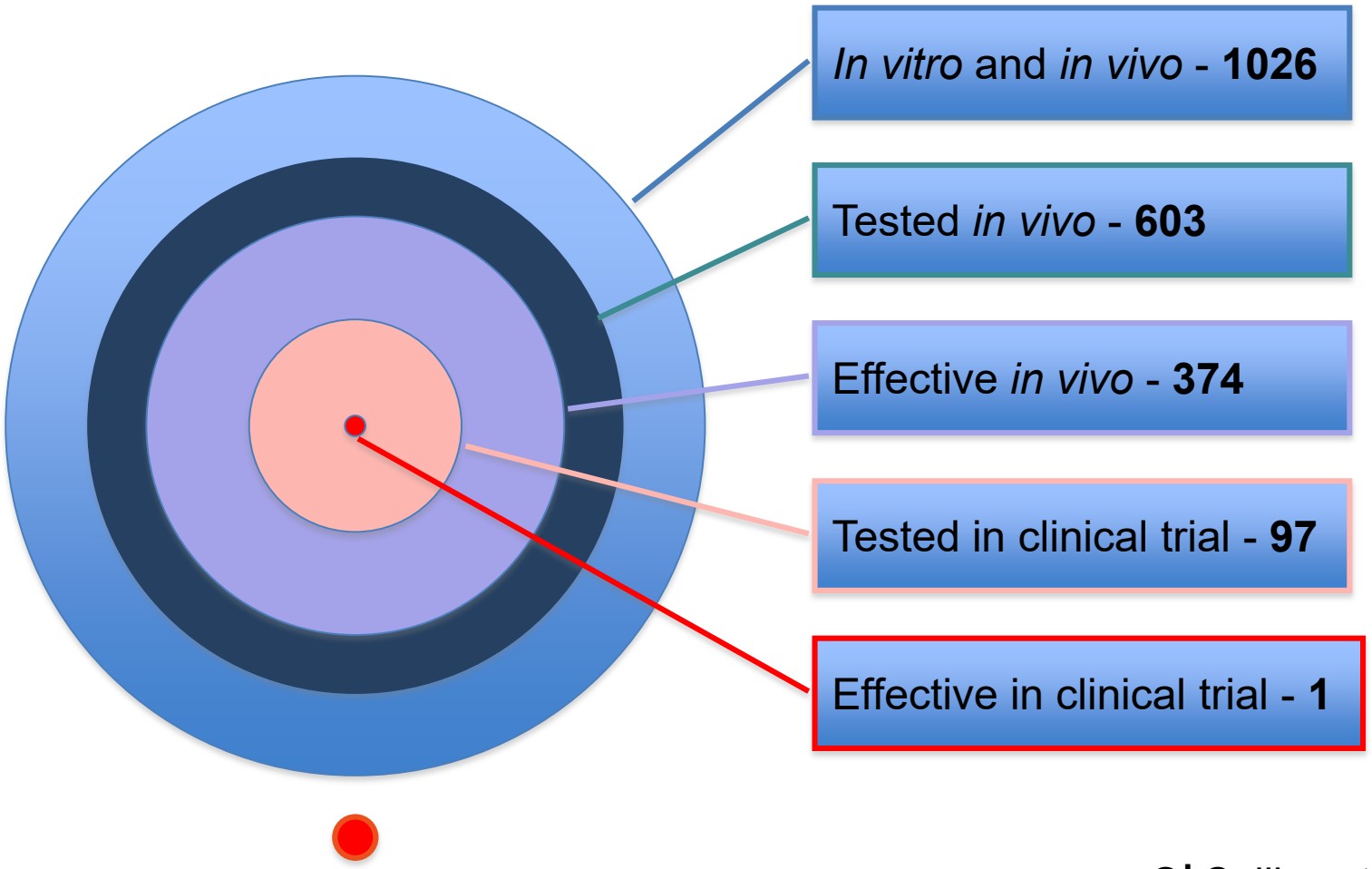

- I have applied and have received grant funding (& will continue) for this research

# My perspective

# Structure

- Scale of the problem 
  - How the life cycle of a preclinical research study is not fit for purpose
- In an ideal world 
  - As a consumer of preclinical research what do I want
- Potential solutions 

# What is translational failure?




O' Collins et al, 2006

# Hypotheses

- In the life sciences there are perverse incentives (publication, funding, promotion) to produce positive results with little attention paid to their validity
- In the use of animal disease models, pressure to reduce the number of animals (cost, time, ethics, feasibility) results in studies either being underpowered or of unknown power
- These factors combine to compromise the utility of animal models and contribute to translational failure

# Translational failure

**Improving the translational hit of experimental treatments in multiple sclerosis**

*Multiple Sclerosis*
0(00) 1–12

DOI: 10.1177/1352458510379612
msj.sagepub.com

Hanna M. Ve
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PAIN® 154 (2013) 917–926

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ORIGINAL ARTICLE

Animal mo

Gillian L. Curri
Hanna M. Vest

Treatment of Intracerebral Hemorrhage in Animal Models: Meta-Analysis

Review

Cell PRESS

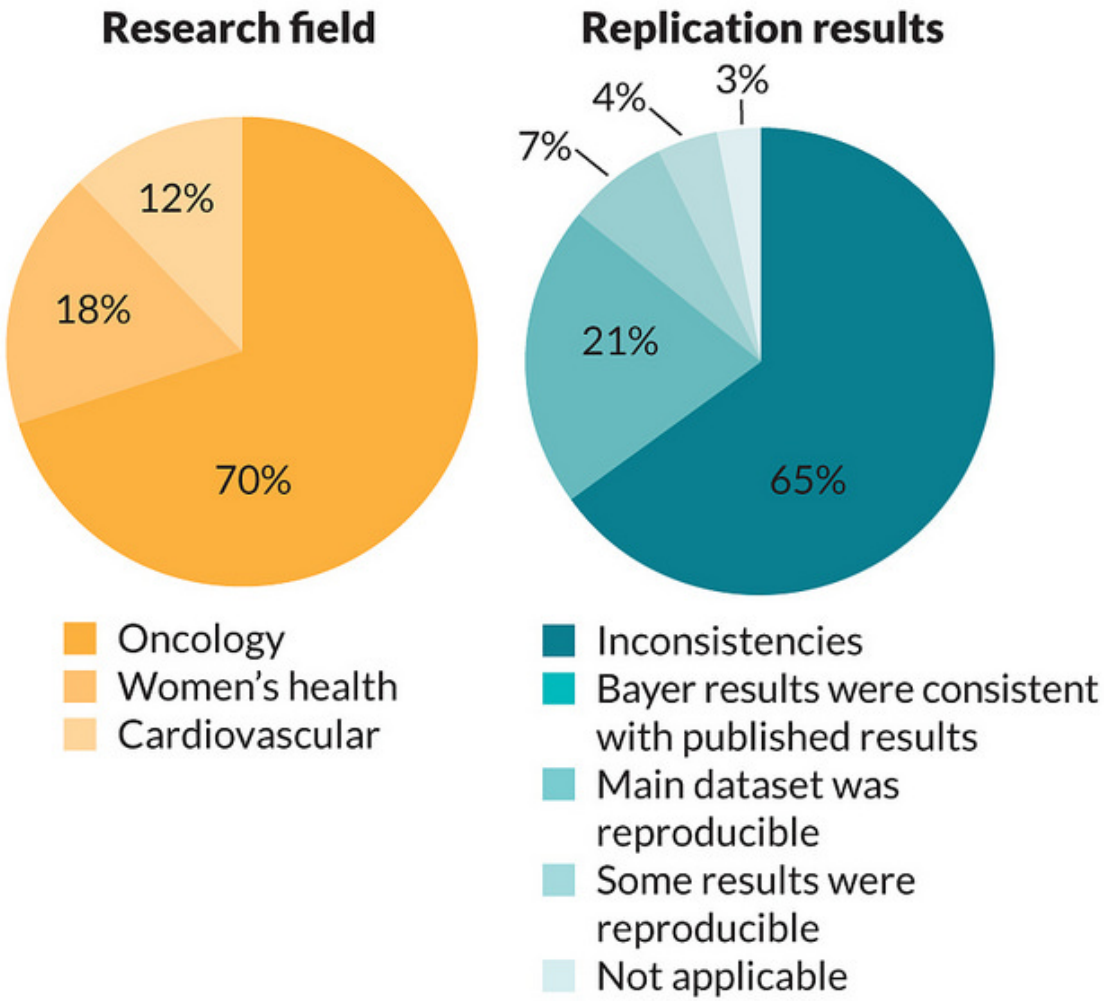
**'Too much good news' – are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease?**

Kathleen R. Zahs[1,2,4] and Karen H. Ashe[1,2,3,5]

[1] N. Bud Grossman Center for Memory Research and Care
[2] Department of Neurology
[3] Department of Neuroscience
[4] Department of Integrative Biology and Physiology, University of Minnesota Medical School, Minneapolis, MN 55455, USA
[5] Geriatric Research Education Clinical Center, Minneapolis VA Medical Center, Minneapolis, MN 55417, USA

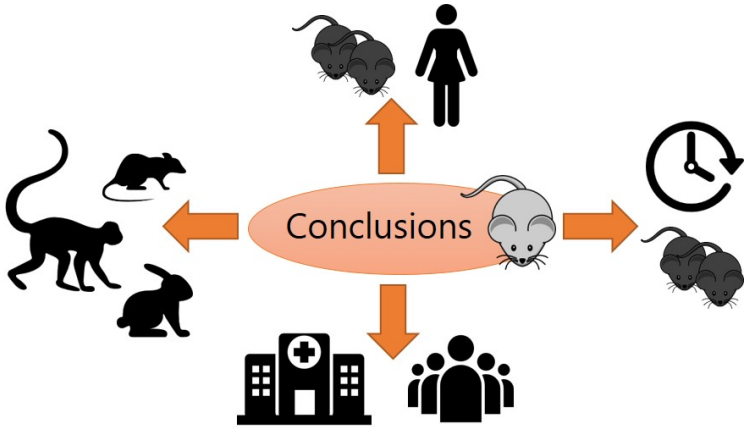
# What happens when pharma tries to replicate academic findings?

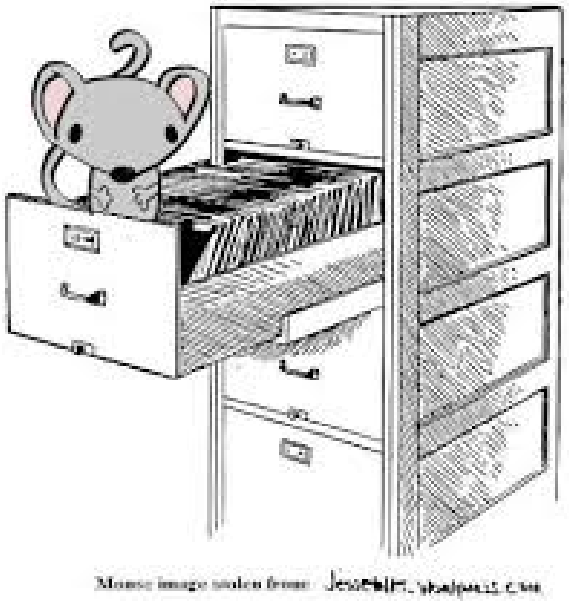
- Bayer, Berlin
- 67 in-house projects over 4 years




Prinz *et al*, Nature Reviews Drug Discovery, 2011

# Potential sources of bias in animal studies

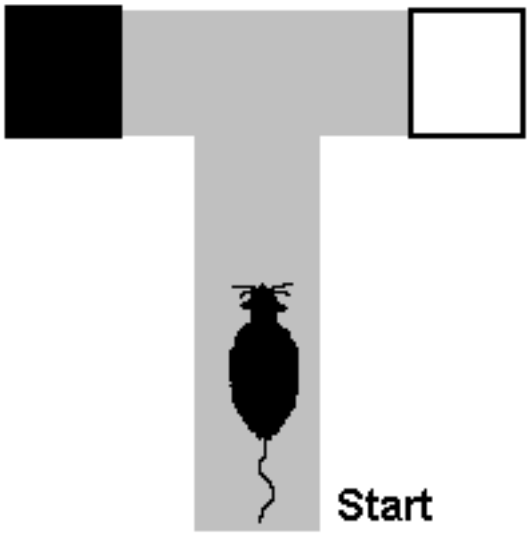


Is the File-Drawer Infested With Mice?

# You can usually find what you're looking for …

- 12 graduate psychology students
- 5 day experiment: rats in T maze with dark arm alternating at random, and the dark arm always reinforced
- 2 groups – "Maze Bright" and "Maze dull"



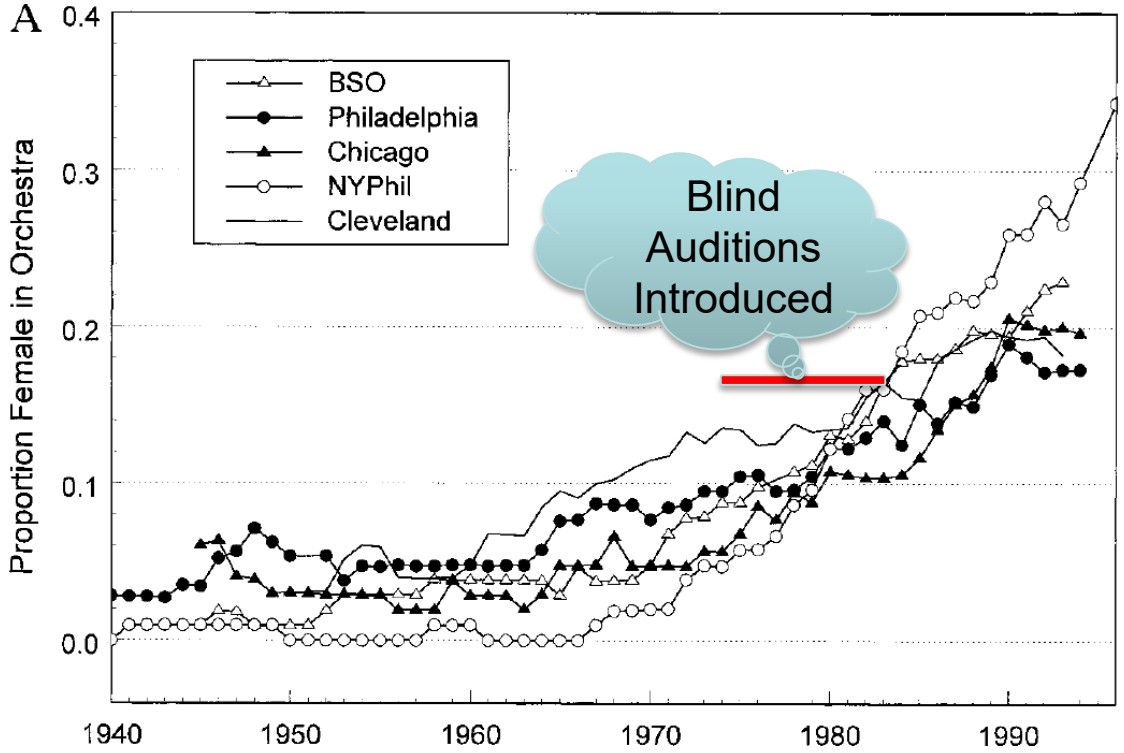

| Group | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|---|---|---|---|---|---|
| "Maze bright" | 1.33 | 1.60 | 2.60 | 2.83 | 3.26 |
| "Maze dull" | 0.72 | 1.10 | 2.23 | 1.83 | 1.83 |
| Δ | +0.60 | +0.50 | +0.37 | +1.00 | +1.43 |

Rosenthal and Fode (1963), Behav Sci 8, 183-9

# Zubin Mehta

Conductor of the LA Symphony (1964-1978) and NY Philharmonic (1978-1990) credited with saying, ***"I just don't think women should be in an orchestra."***

*www.curt-rice.com*

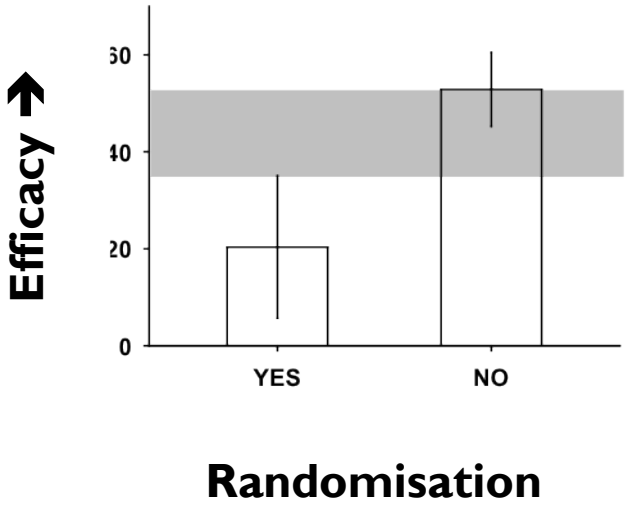



*Goldin & Rouse (2000) American Economic Review 90: 715*

Blind auditions explain ca. 30% of the increase in the female proportion of "new hires" at major symphony orchestras in the US

# Bias is prevalent and important

| | Randomisation | Blinded Outcome Assessment |
|---|---|---|
| Stroke | 36% | 29% |
| MND | 31% | 20% |
| AD | 15% | 25% |
| PD | 12% | 15% |
| EAE | 8% | 15% |
| Glioma | 14% | 0% |

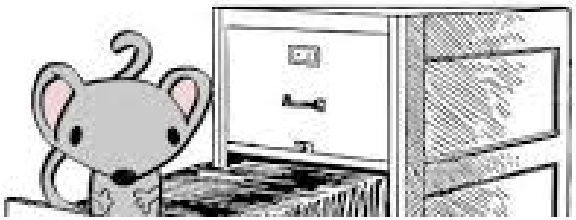



Sena et al *TiNS* 2007

# The umbrella of reporting bias

Not all outcomes and *a priori* analyses are reported

- Publication bias
  - Neutral and negative studies
  - Time lag/remain unpublished
  - Less likely to be identified
- p-hacking
  - Selective analysis
  - Selective outcome repo

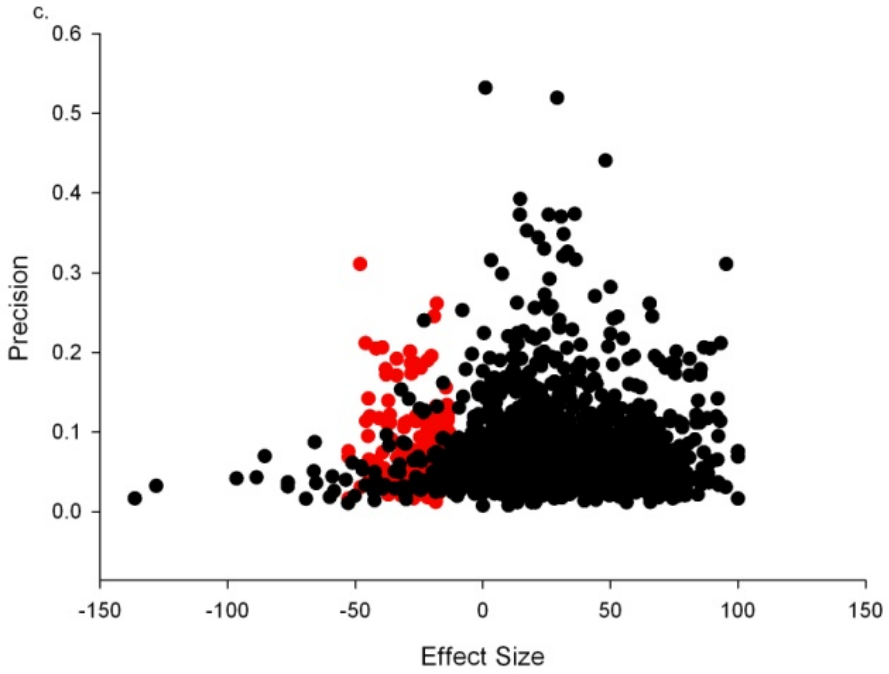


OPEN ACCESS Freely available online

PLOS BIOLOGY

# Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena[1,2,3], H. Bart van der Worp[4], Philip M. W. Bath[5], David W. Howells[2,3], Malcolm R. Macleod[1,6]*




- Overall efficacy was reduced from;
  - **32%** (95% CI 30 to 34%) to **26%** (95% CI 24 to 28%)
- 16% of experiments remain unpublished

# Ideally……

- Preclinical research will benefit from open science tools that facilitates:
  - Clarity of how studies were performed
    - Robustness/replication
  - Collaborative studies
    - External validity
  - Confirmation that studies report what they set our to do
    - Reporting biases
  - Access to data that can be used and compared efficiently
    - Robustness/replication

# How were the data generated?

OPEN ACCESS Freely available online

PLOS BIOLOGY

Perspective

## Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research

Carol Kilkenny[1]*, William J. Browne[2], Innes C. Cuthill[3], Michael Emerson[4], Douglas G. Altman[5]

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

- Journals
- Funders
- Universities
- Learned societies

ARRIVE

### The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

[1]The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK, [2]School of Veterinary Science, University of Bristol, Bristol, UK, [3]School of Biological Sciences, University of Bristol, Bristol, UK, [4]National Heart and Lung Institute, Imperial College London, UK, [5]Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

| | ITEM | RECOMMENDATION | Section/ Paragraph |
|---|---|---|---|
| Title | 1 | Provide as accurate and concise a description of the content of the article as possible. | |
| Abstract | 2 | Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study. | |
| **INTRODUCTION** | | | |
| Background | 3 | a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.<br>b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology. | |
| Objectives | 4 | Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. | |
| **METHODS** | | | |
| Ethical statement | 5 | Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research. | |
| Study design | 6 | For each experiment, give brief details of the study design including:<br>a. The number of experimental and control groups.<br>b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when).<br>c. The experimental unit (e.g. a single animal, group or cage of animals).<br>A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out. | |
| Experimental procedures | 7 | For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example:<br>a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).<br>b. When (e.g. time of day).<br>c. Where (e.g. home cage, laboratory, water maze).<br>d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used). | |
| Experimental animals | 8 | a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range).<br>b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naive, previous procedures, etc. | |

The ARRIVE guidelines. Originally published in *PLoS Biology*, June 2010[1]

# Open Methods

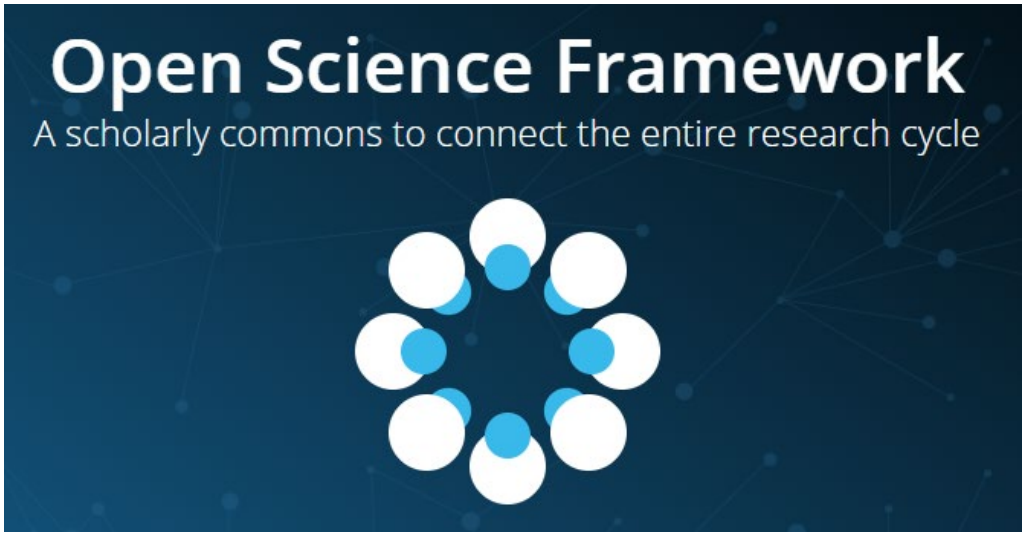
protocols.io

Resource Identification Initiative

# Study protocol registries

NIH U.S. National Library of Medicine
ClinicalTrials.gov

PRECLINICALTRIALS.EU
International register of preclinical trial protocols



# Registered Reports

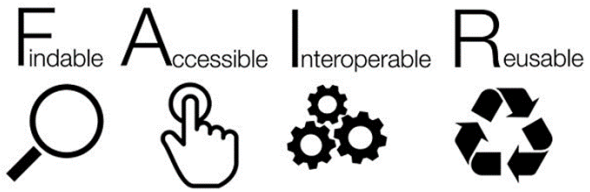
*"Because the study is accepted in advance, the incentives for authors change from producing the most beautiful story to the most accurate one."*

# Allow others to check your work

- Data should be available

figshare DRYAD MENDELEY DATA Put your research data online today zenodo

- Undocumented data dumps
  - No quality control
  - Often not linked to original study
  - How to re-analyse?



# Publish data

SCIENTIFIC DATA

*Scientific Data* aims to **promote wider data sharing and reuse, as well as credit those that share their data** and is open to submissions from a wide range of areas in the natural, clinical and social sciences – including descriptions and analysis of big and small data, from major consortiums, single labs and individuals.

BMJ Open Science

Data descriptor articles

*BMJ Open Science* will consider data descriptor articles of preclinical studies or studies relevant to preclinical research. These articles should describe scientific data to facilitate data-sharing and reuse; their focus is to enable others to reuse data rather than presenting new hypotheses, analyses or interpretations. Descriptor articles combine traditional narrative content with curated structured metadata. Data descriptor articles should include detailed descriptions of the methods used to collect the data and technical analyses to support the quality of data acquisition. Peer review evaluates the rigour with which experiments were conducted during data acquisition. Data must be stored in public and permanently available community-recognised repositories (e.g. Dryad, Figshare).

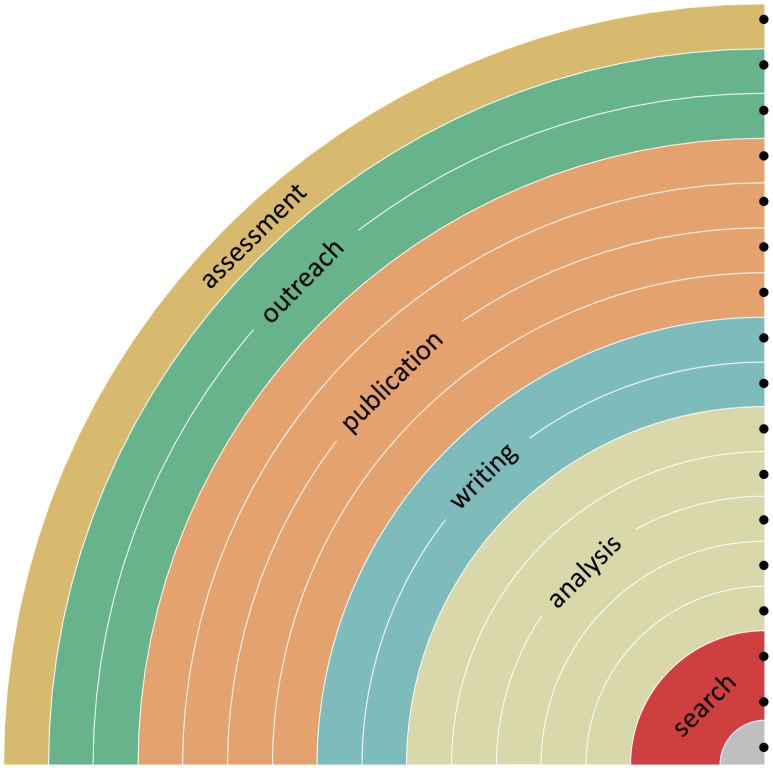
# Who did what?

ORCID

CRediT

| Contributor Role | |
|---|---|
| Conceptualization | Resources |
| Data Curation | Software |
| Formal Analysis | Supervision |
| Funding Acquisition | Validation |
| Investigation | Visualization |
| Methodology | Writing – Original Draft Preparation |
| Project Administration | Writing – Review & Editing |

# THE open workflow




- adding alternative evaluation, e.g. with altmetrics
- communicating through social media, e.g. Twitter
- sharing posters & presentations, e.g. at FigShare
- using open licenses, e.g. CC0 or CC-BY
- publishing open access, 'green' or 'gold'
- using open peer review, e.g. at journals or PubPeer
- sharing preprints, e.g. at OSF, arXiv or bioRxiv
- using actionable formats, e.g. with Jupyter or CoCalc
- open XML-drafting, e.g. at Overleaf or Authorea
- sharing protocols & workfl., e.g. at Protocols.io
- sharing notebooks, e.g. at OpenNotebookScience
- sharing code, e.g. at GitHub with GNU/MIT license
- sharing data, e.g. at Dryad, Zenodo or Dataverse
- pre-registering, e.g. at OSF or AsPredicted
- commenting openly, e.g. with Hypothes.is
- using shared reference libraries, e.g. with Zotero
- sharing (grant) proposals, e.g. at RIO



DOI: 10.5281/zenodo.1147025

# How I do….

- My research has directly influenced my polices as an EiC
  - Will publish sound science irrespective of results
  - Encourage replication studies, preprints and protocol sharing
  - Publish registered reports
  - Use open peer review, open access
  - Publish reviewing history
  - Require open data & RRIDs
  - TOP guidelines, FAIR data principles & OSF badges
  - Use CRediT author contribution taxonomy, ORCiD
  - Require ARRIVE but separately check Landis 4

# Benefits of open science

- For science
  - Improved transparency of research that is more verifiable, efficient, reproducible and sustainable
- For society
  - can readily gain access to, and use, scientific information
- For researchers
  - More citations, more visibility, increased rigour and transparency of their work, better documentation

# Obstacles to researchers…..

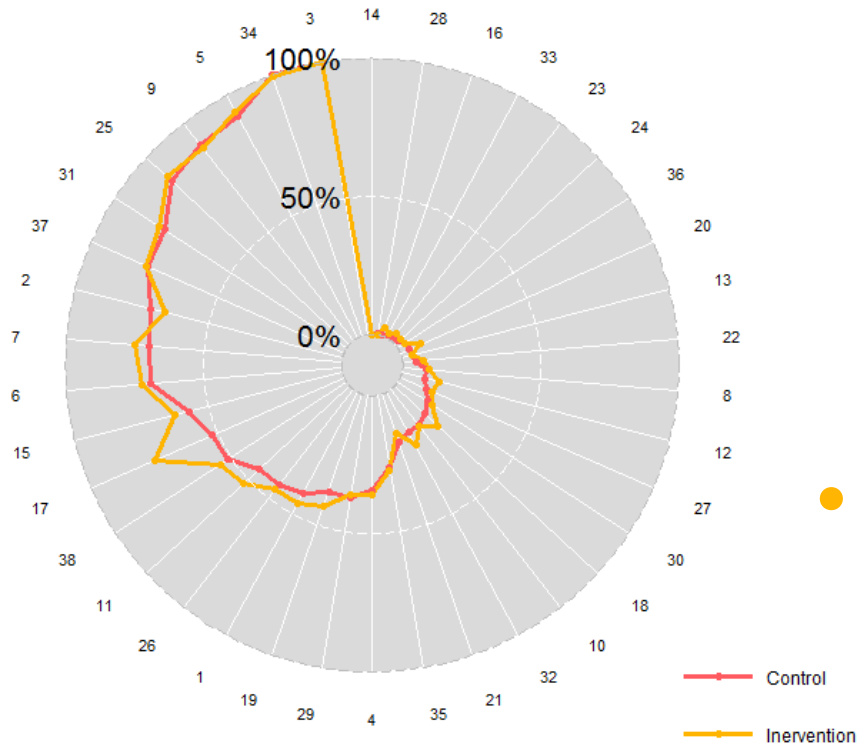
- Limited
  - Emphasis of rigour in grant award
  - Emphasis of rigour in appointment panels
  - CPD opportunities for scientists

# Effectiveness of research improvement

- **Research Improvement Activity:** Things done by stakeholders to increase the usefulness of research with which they are associated

- Important to assess whether interventions can be effectively delivered
- Important to assess whether interventions improve research quality and reduce waste

# RCT - ARRIVE guidelines




- Control:
  - 100% compliance n=0 manuscripts
  - Median compliance 36.8% (29.7-42.1) of relevant items
- Intervention:
  - 100% Compliance n= 0
  - Median compliance 39.5% (31.6-44.7) of relevant items

# Key messages

- *In vivo* studies which do not report simple measures to avoid bias give larger estimates of treatment effects
- Most *in vivo* studies do not report simple measures to reduce bias
- Publication and selective outcome reporting biases are important and prevalent
- Intervention at reporting stage only is too late
- You can only find these things out by studying large numbers of studies
- Any experimental design can be subverted; what's important is knowing how to recognise when this has happened

# Finally……

- Some (useful) tools exists
  - I'm a little confused
- Development/implementation needs resource
- Research is required to determine their efficacy
- Education will help, including training in critical appraisal
- Reward/incentives will likely drive change

# Thanks to.....


Wissenschaftskolleg zu Berlin
INSTITUTE FOR ADVANCED STUDY

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

wellcome

MRC Medical Research Council

ljaf laura and john arnold foundation